REMARKS

Applicants respectfully request reconsideration of the present Application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1, 2, 5-10, 24-25, and 28-48 are pending. Claims 1 and 24 are currently amended. Claims 3, 4, 11-23, 26-27 were previously canceled. Thus, claims 1, 2, 5-10, 24-25, and 28-48 remain pending and are presented for examination.

Support for the amendments to Claims 1 and 24 can be found throughout the specification and claims as originally filed, in particular in ¶¶ [0009], [0010], [0032], [0033], [0034], [0038], and Table 2. No new matter has been added, and entry of the present amendments is respectfully requested.

Claim Rejections under 35 U.S.C. § 103

Dower et al.

Claims 1, 2, 6-9, 24, 25, 30-32, and 37-48 are rejected under 35 U.S.C. § 103 as allegedly unpatentable over Dower et al. (U.S. Patent No. 6,140,493, hereinafter Dower). This rejection is improper because no *prima facie* case of obviousness has been established.

Requirements for a prima facie case of obviousness

Obviousness under 35 U.S.C. §103(a) is a question of law based on underlying factual inquiries. According to the MPEP, the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness by factual inquiries to: (1) determine the scope and content of the prior art; (2) ascertain the difference between the claimed invention and the prior art; and (3) resolve the level of ordinary skill in the pertinent art. (MPEP §2142, citing *Graham v. John Deere Co.* (383 U.S. 1, 148 USPQ 459 (1966)) and *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d, 1385, (2007), hereinafter "*KSR*") "Once the findings of fact are articulated, Office personnel must provide an explanation to support an obviousness rejection under 35 U.S.C. 103." (MPEP§2141 (II))

"[R]ejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (MPEP §2142, quoting *In re Kahn*, 441 F.3d 977, 988, 78

USPQ2d 1329, 1336 (Fed. Cir. 2006). The Supreme Court in *KSR* identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" set forth in *Graham*, and for each rationale, the examiner is required to articulate specific findings and reasoning to establish that a claim is properly rejected. (MPEP §2141 (III); §2143).

Prior art cited in Office Action

With respect to determining the scope and content of the prior art, Dower is cited for disclosing "a method of synthesizing random oligomers with identification tags to screen for desired properties." (Office Action (OA) page 3, lines 5-6) Dower is further cited for disclosing the use of "alphanumeric tags to identify each position of oligomers" (OA page 3, lines 9-11) where the number of probes can be larger than the number of distinguishable detectable labels. (OA page 3, lines 14-18). Dower is cited for allegedly disclosing additional claim features recited in dependent claims. (OA page 3 at line 19 to page 4, line 16)

It is admitted that Dower does not teach the synthesis of oligonucleotide probes, or oligonucleotides of identical length of from 10 to 50 nucleotides, or a reaction mixture comprising an isolated population of labeled probes and a target nucleic acid. (OA page 4, lines 17-20). In fact, Dower discloses oligomers of a variety of different types of monomers. The working examples in Dower discloses stochastic synthesis on bead supports of various peptide oligomers, as well as screening of various peptide oliogmers for binding to a target, and identifying peptide oligomers bound to a target.

Difference between the claimed invention and the prior art

The claim invention is directed to, *inter alia*, populations of labeled oligonucleotide probes comprising different labeled oligonucleotide probes, and reaction mixtures comprising isolated populations of labeled oligonucleotide probes comprising different labeled oligonuelcotidc probes, wherein each labeled oligonucleotide probe comprises an oligonucleotide having n bases, associated with a tag comprising a series of detectably distinguishable signal molecules wherein each detectably distinguishable signal molecule encodes the basc information for a position of the oligonucleotide and comprises at least one copy of a unique signal molecule, a total number of the labeled oligonucleotide probes in the

population being greater than a total number of the detectably distinguishable signal molecules in the population, wherein a first detectably distinguishable signal molecule is used to encode the base information for the first nucleotide of the oligonucleotide of said each labeled oligonucleotide probe, a second detectably distinguishable signal molecule is used to encode the base information for the second nucleotide of the oligonucleotide of said each labeled oligonucleotide probe, and so on until an n^{th} detectably distinguishable signal molecule is used to encode the base information for the n^{th} nucleotide of the oligonucleotide of said each labeled oligonucleotide probe, wherein the copy number and type of unique signal molecules in the detectably distinguishable signal molecule at each position in the tag indicates the base present in each position of the oligonucleotide of said each labeled oligonucleotide probe, and the intensity and type of detectably distinguishable signal molecules in the tag identifies the oligonucleotide.

Merely citing Dower for disclosing the synthesis and use of oligomers that can have identifier tags that can identify the sequence of monomers in the oligomer, is not sufficient to support a conclusion that the claimed invention is obvious over the cited references.

As admitted in the Office Action, Dower does not teach the synthesis of oligonucleotide probes. (OA page 4, line 17) In contrast, the claimed invention is directed to populations of labeled oligonucleotide probes.

As noted in the Office Action, Dower teaches that each detectable label is present once. (OA page 3, lines 19-20) Because Dower discloses a stochastic method for synthesizing random oligomers, a distinct couple step-specific tag for each monomer at each synthesis step, is required as illustrated in Figure 2. In contrast, in the claimed invention, each unique signal molecule can be present up to 4 times per labeled oligonucleotide probe.

Conclusion of obviousness

According to the Office Action, it would allegedly have been obvious to make different labeled oligonucleotide probes of 10-20 nucleotide in length, and to use the oligonucleotide probes in a reaction mixture with a target nucleic acid. (OA page 5 at lines 3-9) According to the Office Action, a skilled person would have been motivated, with a reasonable expectation of success, because Dower allegedly suggests using beads with oligomers attached can be used to screen a library for specific properties, or in receptor screening assays, which the Office Action

proposes that "[t]he hybridization of a target nucleic acid (receptor) with its complement (oligonucleotide probe) can be considered as a receptor screening as it is identifying sequences that specifically bind to the target nucleic acid, and it is also screening the labeled oligonucleotide probe for a specific property, the ability to hybridize with its complement." (OA page 5, lines 9-17)

As noted above, "[r]ejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (MPEP §2142, *supra*) Not only does the Office Action fail to provide articulated reasoning with some rational underpinning to support the legal conclusion of obviousness, but deficiencies in Dower would preclude a conclusion of obviousness.

The cited prior art is deficient because applying the disclosures in Dower for stochastic methods for synthesizing random oligomers that can include the use of an identifier tag to identify the sequence of monomers in each random oligomer, would not yield the claimed invention. Furthermore, one skilled in the art would not be motivated to modify the teachings of Dower to arrive at the claimed invention, much less have a reasonable expectation of success from any attempt at such modifications.

One skilled in the art would not rely on the disclosure in Dower to develop the populations of labeled oligonucleotide probes of the present invention. As admitted in the Office Action, Dower does not teach the synthesis of oligonucleotide probes (OA page 4, line 17). Dower discloses oligomers of a variety of different types of monomers, and the working examples disclose the synthesis on glass beads of peptide oligomers with fluorescent tags (Example 1), the synthesis on glass beads of peptide oligomers with oligonucleotide tags attached (Example 2), parallel synthesis on bifunctional beads of peptide oligomers and oligonucleotide oligomers of "codons" that represent the identity of the amino acid added in each synthesis step (Example 3), and screening of libraries of random peptide oligomers (Examples 4, 5). These detailed disclosures would not motivate a skilled person to modify these methods to prepare the claimed populations of labeled oligonucleotides.

One skilled in the art would not consider the hybridization of a target nucleic acid with its complementary oligonucleotide probe, to be receptor screening using random oligomers as disclosed in Dower. Dower does not teach or even suggest stochastic synthesis of random oligonucleotides with sequence-specific identifier tags, and does not teach or suggest screening a population of random oligonucleotides having sequence-specific identifier tags for hybridization with a target nucleic acid. A skilled person would not rely on the disclosure in Dower of screening peptide libraries for binding to a target, followed by identifying the peptides that bound a target, to make the claimed populations of labeled oligonucleotide probes. Thus, a skilled person would not be motivated to modify the teachings of Dower to make the claimed populations of labeled oligonucleotide probes.

Furthermore, Dower requires a distinct couple step-specific tag for each monomer at each synthesis step during the stochastic synthesis process, such that each detectable label is present once. In contrast, in the claimed invention, each unique signal molecule can be present up to 4 times per labeled oligonucleotide probe. Thus, a skilled person would not be motivated to modify the methods of Dower to produce the claimed populations of labeled oligonucleotide probes, and the skilled person would have no reasonable expectation of success from any attempted modification.

Because no case of *prima facie* obviousness have been established, the rejection is improper and should be withdrawn.

Dower in view of Bawendi et al. and Han et al.

Claims 5, 9, 10, 28, and 34-36 are rejected under 35 U.S.C. § 103 as allegedly unpatentable over Dower as applied to claims 1, 2, 6-9, 24, 25, 30-32, and 37-48, and further in view of Bawendi *et al.* (U.S. Patent Publication No. 2002/0160412, hereinafter Bawendi) and Han et al. (*Nature Biotechnology,* 2001, 19: 631-635, hereinafter Han).

Dower is deficient as a primary reference for the reasons set forth above, and neither Bawendi nor Han cure the deficiencies in Dower. Therefore, because the cited prior art cannot be relied upon to support a conclusion of obviousness, the rejection is improper and should be withdrawn.

CONCLUSION

Claims 1, 2, 5-10, 24-25, and 28-48 are pending. Claims 1 and 24 are currently amended. Claims 3, 4, 11-23, 26-27 were previously canceled. Thus, claims 1, 2, 5-10, 24-25, and 28-48 remain pending and are presented for examination.

In view of the foregoing amendments and remarks, applicant believes the pending application is in condition for allowance, and a notice indicating the allowability of the claims is respectfully requested.

Applicants believe no fees are due. If fees are due, the Director is authorized to charge any fees necessary and/or credit any overpayments to Deposit Account No. 03-3975, referencing Docket No. 043395-0377942.

Respectfully submitted,
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